37. (amended) An adenovirus according to claim 36, wherein the E4 genes have been rendered non-functional by deletion of [all or part of the coding region, and/or] all or part of the promoter region for E4 transcription.

39. (amended) An adenovirus according to claim 38 wherein the E4 genes have been rendered non-functional by genetic modification(s) within regions responsible for the expression or transcriptional regulation, or both, whereby production of said genes is regulatable [according to a desired mode of regulation].

REMARKS

Claims 1-3, 6 and 9-39 are pending in the application. 36, 37 and 39 have been amended in order to more particularly point out and distinctly claim that which Applicants regard as the invention. These claims are supported by page 4, lines 6-15, page 9, lines 8-17 and page 10, lines 4-8 and 15 of the specification.

No new matter has been added. All of the claims under consideration, as amended, are presented as an Appendix attached hereto.

Summary of the Office Action

Applicants acknowledge with appreciation the Examiner's statement that claim 31 is considered allowable. Office Action at page 3.

- Claims 34 and 35 stand rejected under 35 U.S.C. § 112, second paragraph.
- Claims 1-3, 9, 10, 12, 13-16, 17, 18, 19-30, 33, 37, and 39 stand rejected under 35 U.S.C. § 112, second paragraph.
- Claims 36-39 stand rejected under 35 U.S.C. § 102(b) over Berkner et al., 1988, BioTechniques 6:616 (hereinafter "Berkner).

For the reasons set forth below, Applicants submit that all of the claims satisfy the criteria for patentability, particularly under 35 U.S.C. §§ 112 and 102, and are in condition for allowance.

Discussion of Rejections Under 35 U.S.C. § 112

Applicants respectfully traverse the rejection of claims 34 and 35 under § 112, first paragraph. In particular, the Examiner has stated that "[r]egarding the phrase 'wherein the E2 gene or part thereof is the sole adenoviral gene' is vague and unclear because the other listed sequences: the ITR, the encapsulation sequence are adenoviral genes" (Office Action, page 2). Applicants submit respectfully that in this interpretation of the term "gene" the

Examiner is mistaken. The ITR and encapsulation sequences are parts of the adenovirus genome, but they are not genes, not at least as the term "gene" is understood in the art (region of genome coding for a RNA molecule, *e.g.*, mRNA, rRNA, or tRNA). The specification distinguishes these components of the genome from genes as well: "Their genome comprises especially an inverted repeat sequence (ITR) at their end, an encapsulation sequence, early genes and late genes (cf Figure 1)" (page 2, lines 2-5).

With respect to the term "region," which, contrary to the Examiner's statement, is supported by the specification, Applicants submit that this term more accurately characterizes E2 and E4, which are regions of the adenovirus genome that contain a number of open reading frames, *e.g.*, multiple genes. The term region, with reference to early gene coding regions of adenovirus, is found on page 2, line 17, page 3, lines 24-26 ("The vectors of the invention are also very advantageous since they possess very few functional viral regions"), and page 28, lines 21-22 ("E1 (sic, ,) E3, L5 and E4 regions). The Examiner's attention is further invited to the review by Berkner, which refers to the E2 and E4 regions (see page 616, second column referring to the "... early (E) regions 1-4...").

In view of the foregoing remarks, Applicants submit that the Examiner's rejection is overcome and should be withdrawn.

With respect to claim 37, the Examiner contends that the phrase "all or part of and/or all or part of" is confusing. In response, Applicants have deleted the first phrase from claim 37. Thus, this basis for rejection is obviated.

With respect to claim 39, the Examiner contends that the phrase "whereby production of said genes is according to a desired mode of regulation" is ambiguous if the E4 region has been rendered nonfunctional. Applicants respectfully submit that the term "nonfunctional" as used in the specification includes the situation where the adenovirus is modified:

> outside the coding region, and for example in the regions responsible for the expression and/or transcriptional regulation of the said genes. The non-functional character of the said genes can therefore manifest itself by the production of an inactive protein because of structural or conformational modifications, by the absence of production, by the production of a protein having an altered activity, or alternatively by the production of the natural protein at an attenuated level or according to a desired mode of regulation.

Thus, the instant specification clearly envisions regulated expression of the region rendered non-functional. Claims 36 and 39 have been amended accordingly to clarify this point. In view of this amendment and the accompanying remarks, Applicants submit that the Examiner's rejection is obviated and should be withdrawn.

The Examiner alleges that claim 1 is not patentably distinct from claim 36. Applicants disagree respectfully. In claim 1, the E1 genes have been rendered non-functional by deletion, and the E2 or E4 genes have been rendered non-functional by deletion. In contrast, in claim 36, the E4 genes have been rendered non-functional. These claims are clearly of different scope, and the Examiner's contention is in error. (Indeed, this error is highlighted by the rejection of claim 36, but not claim 1, over Berkner.)

In view of the foregoing amendments and remarks, Applicants submit that the Examiner's rejection is obviated in part and overcome in part, should be withdrawn.

Discussion of the Section 102 Rejection

Claims 36-39 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Berkner.

Applicants submit that the amended claims 36-39 are clearly directed to adenoviral vectors in which the E4 gene is inactivated outside the coding region. Berkner is a review of the state of development of adenoviral vectors for the expression of heterologous genes. Berkner discloses that nonconditional helper-independent viruses can be generated by insertions in E3 or other nonessential regions, and that conditional helper-independent viruses can be generated by insertions in E1 or E4. These are first generation adenoviral vectors, which have the many disadvantages disclosed in the specification at page 2, lines 12-27. Berkner suggests that the E4 region containing ORFs can be deleted: "[c]learly the ability to dispense with 2-3 Kb in E4 Ad sequences [in the ORFs] would be advantageous in vector development" (Berkner, page 617, first column).

Berkner does not teach how to make or use the recombinant adenoviral vectors of claims 36-39. Berkner provides wishful thinking and an invitation to experiment, but only with deletion of the E4 genes. There is no hint or suggestion to modify the adenovirus backbone outside the coding region.

The legal test for anticipation under 35 U.S.C. § 102 requires that each and every element of the claimed invention be disclosed in a prior art reference in a manner sufficient to enable one skilled in the art to reduce the invention to practice, thus placing the public in possession of the invention. *See W.L. Gore Associates v. Garlock, Inc.*, 721 F.2d 1540, 1554, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); *In re Donohue*, 766 F.2d 531, 226 U.S.P.Q. 619 (Fed. Cir. 1985). Anticipation under 35 U.S.C. § 102 requires identity of invention. *Scripps Clinic & Research Fdn. v. Genentech Inc.*, 927 F.2d 1565, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991). Cf. *Paperless Accounting, Inc. v. Bay Area Rapid Transit Sys.*, 804 F.2d 659, 665, 231 U.S.P.Q. 649, 653 (Fed. Cir. 1986) ("[A] § 102(b) reference 'must sufficiently describe the claimed invention to have placed the public in possession of it'") (quoting *Donahue*, 766 F.2d at 533, 226 U.S.P.Q. at 621). Furthermore, "it is axiomatic that for prior art to anticipate under §102 it has to meet *every element* of the claimed invention." *Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986) (emphasis added). Lacking any teaching of the claimed invention, Berkner cannot anticipate it.

In view of the foregoing amendments and remarks, Applicants submit that the Examiner's rejection is obviated and should be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant application. In the event that a telephone interview would be helpful in advancing the prosecution of this application, Applicants' attorney invites the Examiner to contact the undersigned at the number shown below.

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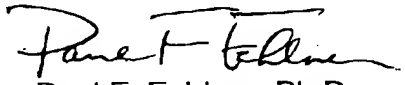
Respectfully submitted,



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APPENDIX
U.S. Patent Application Serial No. 08/397,225
"DEFECTIVE ADENOVIRUS VECTORS AND USE THEREOF IN GENE THERAPY"
RPR File No. EX93015G1-US
Claims Under Consideration

1. (Four Times Amended) A defective recombinant adenovirus comprising

ITR sequences,

an encapsulation sequence, and

a heterologous DNA sequence,

wherein E1 genes have been rendered non-functional by deletion, and wherein E2 or E4 genes have been rendered non-functional by deletion.

2. (Twice Amended) An adenovirus according to claim 1, wherein adenovirus sequences are from a canine adenovirus.

3. (Thrice Amended) An adenovirus according to claim 1, wherein adenovirus sequences are from a human group C adenovirus.

6. (Thrice Amended) An adenovirus according to claim 1, wherein late genes L1-L5 have been rendered non-functional by deletion.

9. (Thrice Amended) An adenovirus according to claim 1, wherein E3 genes have been rendered non-functional by deletion.

10. (Thrice Amended) An adenovirus according to claim 9, wherein L5 has been rendered non-functional by deletion.

11. (Twice Amended) An adenovirus according to claim 1, further comprising a functional E3 gene under the control of a heterologous promoter.

12. (Thrice Amended) An adenovirus according to claim 1, wherein the heterologous DNA sequence is selected from the group consisting of therapeutic genes and genes encoding antigenic peptides.

13. (Four Times Amended) An adenovirus according to claim 12, wherein the heterologous DNA is a therapeutic gene which encodes a product selected from the group consisting of enzymes, blood proteins, hormones, lymphokines, growth factors, neurotrophic factors, apolipoproteins, dystrophin, minidystrophin, tumor suppressor genes, and coagulation factors.

14. (Twice Amended) An adenovirus according to claim 1, wherein the heterologous DNA encodes an antisense sequence.

15. (Twice Amended) An adenovirus according to claim 12, wherein the heterologous DNA encodes an antigenic peptide capable of generating an immune response against microorganisms, tumors, or viruses.

16. (Twice Amended) An adenovirus according to claim 15, wherein the gene encodes an antigenic peptide specific for a virus selected from the group consisting of the Epstein Barr virus, the HIV virus, the hepatitis B virus, and the pseudo-rabies virus.

17. (Twice Amended) An adenovirus according to claim 12, wherein the heterologous DNA sequence further comprises a promoter.

18. (Twice Amended) An adenovirus according to claim 12, wherein the heterologous DNA sequence further comprises a signal sequence.

19. (Twice Amended) A cell line comprising, integrated into its genome, the genes necessary to complement a defective recombinant adenovirus according to claim 1, wherein one of the complementing genes is under the control of an inducible promoter.

20. (Thrice Amended) A cell line according to claim 19, wherein it comprises, in its genome, an E1 gene and an E2 gene wherein the E2 gene is under the control of an inducible promoter.

21. (Thrice Amended) A cell line according to claim 20, wherein it additionally comprises an E4 gene from an adenovirus.

22. (Thrice Amended) A cell line according to claim 19, wherein it comprises, in its genome, an E1 gene and an E4 gene wherein the E4 gene is under the control of an inducible promoter.

23. (Twice Amended) A cell line according to claim 19, further comprising a glucocorticoid receptor gene.

24. (Thrice Amended) A cell line according to claim 19, wherein it comprises E2 and E4 genes and the E2 and E4 genes are under the control of an inducible promoter.

25. (Twice Amended) A cell line according to claim 19, wherein the inducible promoter is an LTR promoter of MMTV.

26. (Thrice Amended) A cell line according to claim 19, wherein it comprises a gene encoding the 72 K protein of E2.

27. (Twice Amended) A cell line according to claim 19, wherein it is obtained from the line 293.

28. (Twice Amended) A composition comprising a defective recombinant adenovirus according to claim 1 and a pharmaceutically acceptable vehicle.

29. (Twice Amended) A composition comprising a recombinant adenovirus according to claim 10 and a pharmaceutically acceptable vehicle.

30. (Twice Amended) A composition according to claim 28 wherein the vehicle is pharmaceutically acceptable for an injectable formulation.

31. (Twice Amended) A defective recombinant adenovirus comprising
ITR sequences,
an encapsulation sequence, and
a heterologous DNA sequence,
wherein E3 and E4 genes have been rendered non-functional by deletion.

32. (Amended) An adenovirus according to claim 31, wherein late genes L1-L5 have been rendered non-functional by deletion.

33. (Amended) A cell line according to claim 19, comprising open reading frames ORF6 and ORF6/7 of E4.

34. (Thrice Amended) A defective recombinant adenovirus consisting essentially of
ITR sequences,
an encapsulation sequence,
a heterologous DNA sequence, and
all or part of an E2 region,
wherein the E2 region or part thereof is the sole adenoviral gene.

35. (Thrice Amended) A defective recombinant adenovirus consisting essentially of
ITR sequences,
an encapsulation sequence,
a heterologous DNA sequence, and
all or part of an E4 region,
wherein the E4 region or part thereof is the sole adenoviral gene.

36. A defective recombinant adenovirus comprising
ITR sequences,
an encapsulation sequence, and
a heterologous DNA sequence,
wherein the E4 genes have been rendered non-functional by modifications outside the coding region.

37. An adenovirus according to claim 36, wherein the E4 genes have been rendered non-functional by deletion of all or part of the promoter region for E4 transcription.

38. An adenovirus according to claim 36 wherein the E4 genes have been rendered non-functional by substitution of one or more bases in the E4 genes.

39. An adenovirus according to claim 38 wherein the E4 genes have been rendered non-functional by genetic modification(s) within regions

responsible for the expression or transcriptional regulation, or both, whereby production of said genes is regulatable.